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March 16, 1999

Office of Generic Drugs
Food and Drug Administration
Department of Health and Human Services
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

Re: Gensia Sicor Pharmaceuticals' ANDA for Ifosfamide (Citizen Petition Docket No. 99P-0129/CP1)

Dear Sir or Madam:

Bristol-Myers Squibb Company ("BMS") is the holder of the approved new drug application ("NDA") for the anticancer drug *IFEX*® (sterile ifosfamide), a dry sterile powder for intravenous injection. BMS submits these comments in opposition to the suitability petition of Gensia Sicor Pharmaceuticals ("Gensia"), filed by the Food and Drug Administration ("FDA") on January 28, 1999 (Docket No. 99P-0129/CP1). Gensia's petition requests a determination by FDA that an abbreviated new drug application ("ANDA") for ifosfamide injection in a "liquid, ready-to-use dosage form," using *IFEX* as the reference listed drug ("RLD"), is suitable for filing.

BMS understands that the Gensia, at the request of FDA, has withdrawn its petition on the grounds that FDA has already approved a "similar" petition. See Letter from Elvia O. Gustavson to Docket Management Branch, March 2, 1999 (attached). Indeed, on May 28, 1998, FDA approved the suitability petition of Mr. Mitchall Clark (Docket No. 98P-0146/CP1), which requested permission to file an ANDA for ifosfamide in premixed aqueous solution.[1] However, FDA approval of a Gensia ANDA for ifosfamide without Gensia going through the full suitability petition process appears to be at odds with the Federal Food, Drug, and Cosmetic Act ("FFDCA") and FDA regulations. See 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93. Furthermore, as described herein, the Gensia petition varies from the Clark petition in important respects that require independent FDA consideration.

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[1] On May 29, 1998, BMS submitted a letter to FDA opposing the suitability petition of Mr. Mitchall Clark (Docket No. 98P-0146/CP1). FDA docketed the BMS letter on June 1, 1998. Since BMS's previous letter was untimely, it is not clear whether FDA gave full, if any, consideration to the problems with the Clark petition raised by BMS.

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As an initial matter, the Gensia petition is so general that it frustrates meaningful public comment and FDA evaluation. FDA should require Gensia to refile its petition and provide more information on its proposed product on the public record, consistent with the policy of openness so important to the suitability petition process.

Additionally, BMS respectfully urges that FDA not approve Gensia's petition for the following reasons:

- First, Gensia's proposed labeling directs that storage of its premixed liquid dosage form should occur at nearly the identical room temperature range that BMS's *IFEX* is stored as a sterile powder. However, BMS has tried to create a premixed aqueous solution of *IFEX*, but found that significant drug instability and degradation changes in the product occurred during normal storage. Even under constant refrigeration, the premixed aqueous solution is not nearly as stable as the dry sterile powder form of *IFEX*.

- Second, since BMS has determined that premixed aqueous solutions of *IFEX* are unstable, a premixed liquid solution of ifosfamide, as proposed by Gensia, is certain to contain ingredients that are not present in *IFEX* in a dry sterile powder form. The presence of additional ingredients such as stabilizers and other excipients not found in *IFEX* raises serious questions regarding both the safety and efficacy of the proposed premixed aqueous solution vis-a-vis the RLD.

- Third, *IFEX* is used only in conjunction with the detoxifying agent mesna, the Gensia petition does not address the fact that its proposed new formulation of ifosfamide does not assure product compatibility with mesna. Therefore, FDA should require Gensia to assess clinically the effect of any difference in excipients for both ifosfamide and mesna.

I. Background

A. *IFEX*

On December 30, 1988, FDA approved BMS's NDA for *IFEX* to treat germ-cell testicular cancer.[2] *IFEX* is manufactured and distributed in the form of dry sterile powder for reconstitution in 1 gram and 3 gram vials. The product labeling indicates that *IFEX* "should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna." The labeling for BMS's brand of mesna affirms the close link between the two drugs: mesna is a

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[2] BMS, a research-based pharmaceuticals company, distributes *IFEX* in the U.S. *IFEX* is manufactured by Asta Medica, a German company, in collaboration with BMS.

detoxifying agent indicated to "reduce the incidence of ifosfamide-induced hemorrhagic cystitis," and is dosed in relation to the ifosfamide dose.

Prior to use, the administering physician dissolves the *IFEX* powder in either Sterile Water for Injection, USP, or Bacteriostatic Water for Injection, USP, to achieve a concentration of 1 gram/50 mL. The labeling directs the user to follow well-established safe handling procedures to protect against accidental exposure of the skin or mucosa to the cytotoxic solution. In the ten years since *IFEX* was approved, BMS has received very few reports of serious injury resulting from handling of *IFEX* in its dry sterile powder form. Additionally, the labeling contains adequate instructions for safely preparing the drug for administration. There is scant evidence of product contamination occurring during constitution of the *IFEX* solution.

In sterile powder form, *IFEX* should be stored at room temperature. *IFEX* solutions that have been constituted or constituted and further diluted should be refrigerated and used within 24 hours.

B. Suitability Petitions

Under section 505(j)(2)(C) of the FFDCA, a person may submit a suitability petition requesting permission to file an ANDA for a drug with a different dosage form from the reference listed drug. 21 U.S.C. § 355(j)(2)(C). FDA must deny a suitability petition if it finds "that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug." 21 U.S.C. § 355(j)(2)(C)(i); 21 C.F.R. § 314.93(e)(1)(i).

FDA regulations note that approval of a suitability petition may not occur if "[a]ny of the proposed changes from the listed drug would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem." 21 C.F.R. § 314.93(e)(1)(iv).

II. A Premixed Solution of Ifosfamide Using an Unidentified Liquid Raises Numerous Potential Problems.

A premixed liquid solution of ifosfamide introduces new concerns about preservation of the product throughout its manufacture, transport, and storage; about safety and efficacy; and about compatibility with concomitant therapies. Since the degradation problems and the storage and distribution requirements of a premixed liquid solution of ifosfamide may need to be addressed through labeling changes to ensure the safe and efficacious use of this particular dosage form, Gensia's petition may not be approved under the FFDCA and FDA regulations.

A. The Gensia Petition Lacks Information Needed for Public Comment and FDA Evaluation.

There are three major omissions in the Gensia Petition that frustrate BMS's -- and FDA's -- ability to assess it. First, the Petition fails to identify the diluent Gensia proposes to use in its ANDA for *premixed* ifosfamide solution. The petition refers mainly to the solution only as a "liquid."[3] Second, Gensia's proposed labeling does not indicate any stability data or shelf life for its premixed dosage form. Rather, it states only that solutions of constituted ifosfamide *that have been further diluted* are "physically and chemically stable for at least 1 week at 30°C or 6 weeks at 5°C." By contrast, the current *IFEX* labeling directs that all solutions of IFEX, whether prepared with sterile or bacteriostatic water and whether reconstituted or reconstituted and further diluted, should be refrigerated and used within 24 hours.[4] Third, the Gensia labeling directs that the premixed solution be kept between 15°C and 30°C (59°F to 86°F), a temperature range that, without explanation, attempts to expand the recommended storage range of 20°C to 25°C (68°F - 77°F) for *IFEX* in sterile powder form.

In light of the problems with degradation associated with a premixed ifosfamide solution (discussed further below), it is incumbent upon Gensia to be more specific, on the public record, concerning the differences between *IFEX* and Gensia's proposed product. Gensia's vagueness makes it impossible for those, such as BMS, who wish to consider and comment on the suitability petition, to have fair notice of the nature of the change at issue. As importantly, FDA will be unable to assess whether additional testing for Gensia's product is warranted, and thus whether to approve Gensia's suitability petition, without more information about its product.

B. Degradation

The Petition suggests that Gensia would employ a "non-preserved diluent." This raises the possibility of a solution of 100% water (even if sterile or bacteriostatic), without other buffers or solvents, such as alcohol. However, BMS's own research (in conjunction with Asta Medica) has indicated that compared to dry sterile powder, ifosfamide in *premixed* aqueous solution experiences substantially more -- and more rapid -- degradation of the active ingredient. This results in the creation of a substantial quantity of unknown impurities. While the amount and rate of product degradation depend upon the storage time and temperature, a premixed aqueous solution is substantially less stable than a sterile dry powder under all conditions.

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[3] It also characterizes its version as a "sterile solution," and makes one oblique reference to the benefits of a "non-preserved diluent" for preconstituting ifosfamide.

[4] The *IFEX* package insert Gensia included with its petition is outdated. The old *IFEX* labeling, which directs that *IFEX* solutions which are not prepared with bacteriostatic water should be refrigerated and used within 6 hours, does not reflect the stability information in the current labeling.

For example, *IFEX* in dry sterile powder degraded less than 1% after 5 years at 26°C. By contrast, even refrigeration of ifosfamide solution at 8°C for two years resulted in up to 10% degradation. By 18 months, there was 6% degradation at 8°C.[5] Importantly, when the premixed solution was kept at 20°C -- the storage temperature indicated in Gensia's proposed labeling -- degradation occurred at the rate of 0.1% *per day*. Given the high rate of degradation BMS observed with a premixed ifosfamide solution, FDA should require Gensia to provide greater explanation of its proposal before making a determination on the Gensia petition.

The high rate of premixed aqueous ifosfamide degradation has potentially serious significance for safety, especially because the identity of a substantial percentage of the degrading material is unknown and variable, depending on the stabilizers or excipients used. While some of the precipitating substances are phosphoric acids, 4% of the impurities were unknown impurities when the solution was kept at 8°C for two years. At 2°C, almost 1% of the precipitating substances were unknown impurities.[6]

Because BMS and Asta Medica -- the companies with the most experience with the product -- have been unable to adequately address this problem, they have put aside their co-development effort for a premixed aqueous dosage form. Accordingly, it is incumbent upon Gensia to conduct studies to characterize and quantify the inevitable unique product degradants of its proposed premixed liquid dosage form and determine how they affect the toxicity, safety, and effectiveness of ifosfamide, so that prescribing physicians have sufficient information about the product.

C. Refrigerated Transport and Storage

As indicated above, the problems with premixed aqueous ifosfamide stability increase in direct relationship with the storage temperature. Thus, to ensure stability and safety, the manufacturer of an aqueous solution would have to ensure the constant refrigeration of its ifosfamide to minimize the degradation from the time of manufacture to the time of administration. Any break

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[5] Even at the colder 4°C, the premixed solution experienced 5% degradation after 18 months.

[6] FDA chemistry review staff, in an unofficial setting, has indicated that certain processes, including "terminal sterilization of a sterile solution," can alter a product's impurity profile. Washington Drug Letter, at 3 (December 12, 1994) (citing comments on impurities guide drafted by the International Conference on Harmonization). This suggests that, even if a premixed liquid dosage form were sterile, and had, at the time of its preparation, a similar impurities profile as *IFEX*, the terminal sterilization of that solution prior to administration could alter the impurities profile, with unknown effects on the product's safety and effectiveness.

in the manufacture/transport/storage chain that subjects the solution to a higher temperature would increase the degradation rate of known and unknown impurities.

The Gensia petition and proposed labeling are silent with respect to refrigeration needs and shelf life/stability issues. If anything, the proposed storage temperature suggests that no refrigeration is needed at all. In light of BMS's experience, Gensia bears the responsibility to demonstrate that the manufacture, distribution, and storage of the premixed aqueous dosage form is truly feasible.[7]

Moreover, because *IFEX* and mesna are ordinarily stored at controlled room temperature prior to reconstitution, the introduction of a dosage form of ifosfamide which requires continual refrigeration could easily cause confusion among administering physicians and their staffs. Such confusion could result in practitioners unknowingly administering to patients product that has degraded due to improper storage.

D. Use of Other Solvents

While the petition proposes a premixed solution, the general lack of descriptive precision in the petition raises the concern that other solvents may also be used in preparing the "liquid" dosage form. While an ifosfamide solution using ethanol or other alcohols may improve product stability over a true aqueous solution, which is 100% water, the use of other solvents would introduce novel toxicity issues for ifosfamide.

The exact formulation of the solution is particularly relevant because mesna is administered in an aqueous solution containing 10.4 mg of benzyl alcohol as a preservative. To the extent that the proposed dosage form of ifosfamide might also utilize alcohol as a preservative, FDA should require additional information about how this additional alcohol level impacts the toxicity of the drug combination. Thus, including alcohol or another buffer in a premixed aqueous solution does not resolve, and may exacerbate, the dosage formulation problem.

E. Interaction and Compatibility Issues When Used with Mesna

As ifosfamide is always administered in combination with mesna, FDA should be especially concerned that a new dosage form may adversely impact the compatibility of the two anticancer drugs. In this case, the requested change in dosage form has implications not just for potential variance in ifosfamide safety and efficacy, but also for potential negative synergy with mesna,

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[7] For example, trucking and warehousing are normally not refrigerated. Transition points, such as loading and receiving docks, where product often sits for hours, pose special problems. Numerous unrefrigerated product moves also occur in the normal hospital environment, with receiving, storage, delivery to the treatment area, set-up for the day's patient treatments, etc.

its therapeutic partner.[8] Just as use of alcohol in a premixed solution of ifosfamide may increase toxicity because mesna's aqueous solution already contains benzyl alcohol, other excipients or inactive ingredients in a premixed liquid solution may increase the toxicity of ifosfamide/mesna therapy.

Furthermore, mesna's labeling states that its administration in combination with ifosfamide makes it difficult to distinguish whether adverse reactions are attributable to mesna, or ifosfamide. FDA should consider whether introduction of a premixed liquid form of one of the combination agents might exacerbate this problem and require reassessment of the known adverse reaction profile.[9]

III. Approval of Gensia's Vague Petition Would Be Inconsistent with FDA's Growing Recognition that Inactive Ingredients and Impurities in Generic Drugs May Affect Safety and Effectiveness.

In 1992, FDA once noted its position that differences in inactive ingredients between a potential generic drug and the reference listed drug are not covered during the suitability petition process. 57 Fed. Reg. 17,950, 17,957 (1992). However, FDA is in fact required to evaluate how a new dosage form affects the safety and effectiveness of active ingredients. Accordingly, where the proposed dosage form introduces different inactive ingredients as part of a product reformulation with resultant demonstrated changes in the product toxicity profile and possible changes in its efficacy in its combination-product use, FDA should legitimately consider the potential effects of those new inactive ingredients when reviewing the suitability petition.

Moreover, recent FDA policy proposals place greater responsibility on ANDA sponsors to evaluate how inactive ingredients affect drug performance, and to identify impurities in generic drugs. Currently, an ANDA may have different inactive ingredients from the RLD, as long as the applicant identifies and characterizes the inactive ingredients, and provides information demonstrating that such differences do not affect product safety. 21 C.F.R. § 314.94(a)(9). On November 19, 1998, FDA issued draft amendments to the regulations, proposing that an ANDA applicant utilizing different

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[8] See, e.g., Sandeep Nema, R.J. Washkuhn, and R.J. Brendel (Mallinckrodt Medical, Inc.), "Excipients and Their Use in Injectable Products," 51 PDA Journal of Pharmaceutical Science & Technology 166 (July-Aug. 1997) (given the unique formulation concerns for injectable products, even where particular excipients have been deemed safe for other products, "there is no guarantee that [a] new [injectable] product will be safe as excipients are combined with other additives and/or with a new drug, creating unforeseen potentiation or synergistic toxic effects").

[9] Similarly, FDA should consider whether Gensia must show that its dosage form is compatible with the fluids often needed to further dilute *IFEX* -- Dextrose, Sodium Chloride, or Lactated Ringer's Injection.

inactive ingredients demonstrate that such inactives do not affect product effectiveness, not just safety. 63 Fed. Reg. 64,222, 64,222-23 (Nov. 19, 1998). FDA stated that the amendment is necessary because "a change in inactive ingredients may affect safety or efficacy or both." Id. at 64,223.

Additionally, FDA issued two draft guidances for industry in 1998 (subsequent to approval of the Clark petition): "ANDAs: Impurities in Drug Products" (December 1998) and "ANDA's: Impurities in Drug Substances" (June 1998). Each of these describe the responsibilities of ANDA sponsors to identify, qualify, and report information on impurities. Indeed, the December 1998 draft Guidance focuses specifically on degradation products of the active ingredient or impurities created when the active ingredient reacts with an excipient. These are the types of impurities that troubled BMS during its own efforts to develop a safe and effective premixed liquid dosage form of *IFEX*. In its petition, Gensia has provided FDA with no information even to determine whether additional testing of the dosage form would be warranted, and thus whether the suitability petition should be approved. In accordance with the agency's increasing attention to potential impact of inactive ingredients and impurities, FDA should not approve Gensia's petition until Gensia provides the information that will allow FDA to make an adequate evaluation of the petition.

III. Conclusion

IFEX is a powerful anticancer drug, given in combination with mesna to treat testicular cancer when other therapies have proven ineffective. Accordingly, FDA should be particularly wary of potential safety problems and changes in clinical effects that could result from the use of a premixed liquid solution of ifosfamide. This is especially the case where, as here, the dosage form at issue has been previously demonstrated to raise actual product safety and efficacy concerns. In light of the foregoing, FDA should require Gensia to refile and supplement its petition with additional information – available for public comment – that will facilitate understanding of FDA and the public on this important issue.

Thank you for your timely consideration of these comments. BMS would be happy to discuss further the issues raised in this letter. In particular, if you would like, we can provide further scientific and clinical support for the safety and efficacy concerns we have noted. You may reach me at (609) 252-3414.

Sincerely,

David T. Bonk
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Worldwide Medicines Group
Bristol-Myers Squibb Company